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Editorial Comment

At Home Thrombolysis*

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The intriguing reports in this issue of the Journal by Weaver et al. (1) from the Myocardial Infarction Triage and Intervention Project (MITI) and by Roth et al. (2) raise a number of important public health issues. Until recently, the model used to explain the benefits of reperfusion therapy promoted the belief that rapid treatment is necessary for any significant treatment effect, because irreversible myocardial necrosis occurs quickly after vessel occlusion (3). In support of this model, data from the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) (4) and the Second International Study of Infarct Survival (ISIS-2) (5) trials demonstrated that the reduction in mortality from thrombolytic therapy was directly related to the time between symptom onset and treatment. In a pioneering study, Koren et al. (6) found an improvement in ejection fraction of 8% units when streptokinase treatment was administered at home rather than delayed until hospitalization. Although we now believe that mechanisms in addition to myocardial salvage explain the improved survival with reperfusion therapy (7–9), very early treatment clearly has the potential to maximize the beneficial effect of this therapy.

Feasibility. The primary finding of the two present reports (1,2) is that at home thrombolysis is feasible. The report of Roth et al. (2) adds to existing data that indicate the practicality of physician administration of thrombolytic therapy in settings where physicians travel in ambulances. The MITI report (1) demonstrates that well trained paramedics, armed with advanced electrocardiographic (ECG) technology, can discriminate those patients with acute myocardial infarction who meet criteria for thrombolytic therapy from the large number of patients with symptoms compatible with myocardial ischemia. Now that at home thrombolytic therapy has been shown to be feasible when administered by physicians and potentially applicable in the much broader population served by paramedics, we must begin to focus on questions related to implementation. Who should be treated? Who should provide treatment? Does the clinical benefit of at home treatment justify the potential risk?

Who should be treated? To find the 107 patients eligible for at home thrombolytic therapy, the Seattle paramedics (1) evaluated 2,472 patients with a stringent set of inclusion criteria. Such a cautious approach seems justified in the first paramedic trial, because an adverse event might jeopardize further evaluation of the concept. However, if at home thrombolytic therapy is to have an important impact, the inclusion criteria must eventually be loosened. In particular, the future clinical practice of at home thrombolytic therapy will probably include patients aged >79 years, >12 h from symptom onset and with a blood pressure difference in the arms and no other evidence for aortic dissection. Treatment of cardiogenic shock should include early thrombolysis and aggressive mechanical efforts to achieve and sustain reperfusion. Preliminary evidence (10) indicates that treatment of patients after cardiopulmonary resuscitation may be especially beneficial. Overall, the number of patients treated would probably be doubled from the numbers in the MITI Project (1).

Who should treat? These reports (1,2) provide an interesting contrast in terms of their potential impact. Given the large number of patients with symptoms compatible with acute ischemia, the system described by Roth et al. (2) seems impractical in most societies. The MITI Project (1) has convincingly demonstrated that paramedics can effectively screen. The full impact and potential liability of paramedic treatment will only be known when the randomized trial (MITI, Phase II) currently in progress is completed. In this phase, patients are being randomized to thrombolytic treatment in the field or at home. Even with the restrictive screening used in this report (1), the intracranial bleeding rate is likely to be at least 0.5% (11). Whether the risk/benefit ratio for this catastrophic complication can be properly weighed by paramedics, especially in the U.S. where litigation is a major issue, remains to be seen. The cost to an emergency medical system of one lawsuit stemming from this possible complication must be weighed against the benefit to society.

Enthusiasm for paramedic therapy may be dramatically increased by the availability of the technology to transmit ECG information by cellular telephone. The potential for ECG systems to augment the knowledge of the paramedic and physician in the early hours of acute ischemia is only

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moderately reached by the system reported. Improvements in cellular telephone capacity should improve transmission, reducing or eliminating the 23% initial and 8% current rate of transmission failure in Seattle. Not addressed in this report (1) is the variability present in the interpretation of the transmitted ECG. A technologic goal should be the development of a 12 lead monitor with a simple method of attachment, continuous acquisition of data in a digital mode and a computerized algorithm to detect changes in QRS and ST segment configuration. Such a system would hold promise not only for rapid diagnosis but also for monitoring during therapy to detect reperfusion or reocclusion (12).

The MITI report (1), together with other recent observations (13,14), documents the extraordinary delay between patient presentation and treatment in U.S. hospitals. As the potential for the paramedic system is further evaluated, one major question is whether rapid diagnosis in the field can lead to a marked decrease in the time to treatment, even if therapy is initiated in the hospital. If the acute event could be diagnosed in the field, the hospital team could be mobilized for evaluation and treatment immediately on the patient's arrival. The development of a plan for rapid diagnosis and subsequent treatment with thrombolytic therapy should become a major priority of all hospitals.

Evaluation of outcome. To make rational decisions about the health policy implications of at home therapy, four types of information are needed: 1) a scientific basis, 2) a demonstration of feasibility, 3) a measurement of health outcomes, and 4) an estimate of costs. The scientific basis and feasibility are already established. The latter two types of information deserve specific comment.

The report of Roth et al. (2) may be disconcerting at first, because no difference in clinical outcome was demonstrated despite a 44 min difference in time to treatment. These results must be interpreted cautiously, for both practical and statistical reasons. The use of global left ventricular ejection fraction as an end point in trials of thrombolytic therapy has been plagued by a series of problems (15): incomplete ascertainment, technically inadequate studies and death before the time when the measurement was planned. Furthermore, Van der Werf (16) has pointed out that, because thrombolytic therapy may be particularly beneficial in patients with the largest amount of damaged myocardium, patients with the worst left ventricular function are more likely to survive in the earlier treated group, leading to a preponderance of low ejection fractions in this group. Patients with poor function in the group treated later may die before the follow-up measurement, thereby increasing the average ejection fraction in this group. Finally, the size of sample necessary to detect differences in ejection fraction must be kept in mind. To have the power adequate (80%) to detect a 4% unit difference in ejection fraction as reported by Roth et al. (2), a total sample size of 320 patients would be necessary. In fact, given the large standard deviation in the measurement by Roth et al. (2) (18% units compared with the usual 10% to 12% units), the authors had only a 20% chance (power) of detecting a meaningful difference.

Table 1. Composite Clinical End Point*

End Point
Death
Stroke
Reinfarction
Heart failure
Severe recurrent ischemia

*Cost included in secondary analysis to provide perspective for health policy decisions.

A second problem evident in the report of Roth et al. (2) is the multiple comparisons of clinical end points made with p values reported as "NS." The proliferation of p values does not serve a useful purpose, because the conventional level of significance ($p < 0.05$) then becomes meaningless. If 20 significance tests are performed on random data, a 64% chance exists that at least one test will be "significant" by the use of conventional p values. Furthermore, a series of differences in baseline characteristics or outcomes, none of which is individually significant, can add up to an important clinical effect (17).

One approach to these problems is to evaluate a series of negative patient outcomes during the period of study and to combine these into a composite clinical end point for statistical comparison. These outcomes can be "disaggregated" (Table 1) for descriptive presentation, a method that has been labeled the "Consumer Reports approach." Among these outcomes should be some measure of cost in either dollars or resources used. This approach allows the study to have a primary end point measured in every patient while preserving a single statistical test for that end point.

Conclusion. A major step forward has been taken in understanding the potential and feasibility of earlier administration of thrombolytic therapy at home. The hard work of demonstrating whether such an approach is beneficial will require carefully planned studies with adequate sample size and measurement of multiple end points. The randomized trial of MITI, Phase II will have these features. Until the evidence is available, communities should be cautious about instituting major programs for at home treatment as a routine practice. Current efforts should focus on reducing unnecessary delay once the patient reaches the hospital.

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